

## **REMARKS**

### **Introductory Comments:**

Claims 1-9 were examined in the Office Action under reply and stand newly rejected under 35 U.S.C. §103(a). This rejection is respectfully traversed as discussed more fully below.

Applicants note with appreciation the withdrawal of the previous rejections under (1) 35 U.S.C. §112, first paragraph (claims 1-10); (2) 35 U.S.C. §112, second paragraph (claims 1-20); and (3) 35 U.S.C. §103(a) (claims 11-20).

### **Request for Withdrawal of Finality:**

The rejection of claims 1-9 under 35 U.S.C. §103(a) is presented here for the first time. However, claim 1 was amended in the last response to incorporate the substance of claim 10. The remaining claim amendments were made in order to spell out abbreviations. Claim 1 is therefore substantively the same as previous claim 10. Claim 10 was not subject to any rejections under 35 U.S.C. §103(a). Applicants therefore do not believe the Office Action is properly made final and respectfully request the withdrawal of the finality thereof.

M.P.E.P. §706.07(a) makes clear that a rejection should not be made final "where the Examiner introduces a new ground of rejection not necessitated by amendment of the application by applicant." (Emphasis added). Since the substance of claim 1 is essentially that of previous claim 10, the Office could have brought this rejection in the last Office Action. Accordingly, the Office cannot now, in the final action, state a new rejection which could have been asserted previously, without giving applicants an opportunity to address the same. Such is an abridgment of applicants' right to due process. Thus, applicants request withdrawal of the finality of the present Office Action.

### **35 U.S.C. §103(a):**

Claims 1-6, 8 and 9 were rejected under 35 U.S.C. §103(a) as unpatentable over Ryan et al., *Immunol. Lett.* (June 1999) 69:59 ("Ryan") in view of EP 0 462 534 to Marsili et al. ("Marsili"). The Office alleges Ryan teaches nasal delivery of an acellular pertussis vaccine combined with LT-K63 or LT-R72. Marsili is said to teach a vaccine comprising an acellular,

non-toxic 9K/129G double mutant of pertussis holotoxin, FHA and a pertussis 69 Kd protein, for use in developing an acellular anti-pertussis trivalent DPT vaccine. The Office concludes “it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace Ryan’s pertactin-containing acellular pertussis vaccine with Marsili’s DTPa combination to produce the instant invention with a reasonable expectation of success.” Office Action, page 4. However, applicants respectfully submit the claims are indeed patentable over the cited combination and traverse the rejection and the Office’s supporting remarks.

The Supreme Court in *KSR Int’l Co. v. Teleflex, Inc.*, No 04-1350 (U.S. Apr. 30, 2007) reaffirmed the viability of the four factual inquiries underlying an obviousness analysis provided in *Graham v. John Deere*, 148 USPQ 459, 467 (U.S. 1966). These factors include: (a) determining the scope and contents of the prior art; (b) ascertaining the differences between the prior art and the claims in issue; (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary considerations. Moreover, the Supreme Court in *KSR* recognized that the “teaching, suggestion, or motivation” analysis provides a helpful insight in determining whether the claimed subject matter is obvious. This analysis is provided in MPEP 2142. In particular, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Additionally, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Both the teaching or suggestion to make the claimed combination, as well as the reasonable expectation of success, must be found in the prior art, not in applicant’s disclosure. See, e.g., *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). Based on the foregoing, applicants respectfully submit the Office has failed to establish a *prima facie* case of obviousness.

The present claims are directed to trivalent mucosal vaccines formulated for intranasal administration. The vaccines include a diphtheria antigen, a tetanus antigen, and an acellular pertussis antigen, as well as LT-K63 or LT-R72 as an immunological adjuvant. The cited art does not teach or suggest this combination. Although Ryan teaches nasally delivered acellular pertussis vaccines formulated with LT-K63 or LT-R72, Ryan does not teach or suggest the

addition of a diphtheria antigen and a tetanus antigen. It is well known that mixtures of antigens can fail to be as effective as individual components due to physical interactions of the individual antigens which might result in altered conformation, aggregation or precipitation.

Immunological dominance or competition between component antigens is also known to occur. See, e.g., Guide for Adult Immunizations, page 119 (appended), evidencing that yellow fever and cholera vaccines cannot be mixed. Finally, the FDA requires that the efficacy of mixtures be shown even if the efficacy of the individual components has been demonstrated, further demonstrating the unpredictable results obtained with mixtures versus individual components. As readily seen, the efficacy of mixed antigen vaccines cannot be predicted.

The Examiner cites Marsili for teaching a trivalent DPT vaccine. However, the trivalent vaccine described by Marsili is formulated with Alum and injected rather than delivered intranasally. See, page 14 of Marsili. Nothing can be gleaned from Marsili regarding the efficacy of a trivalent vaccine formulated for a different route of administration using a different adjuvant as claimed by applicants. The literature is replete with evidence showing that immunological adjuvants have differing mechanisms of action and immune responses to particular antigens are highly dependent on the type of adjuvant selected. See, e.g., Vogel, F.R., *Clinical Infectious Diseases* (2000) 30(Suppl 3):S266-270 (appended). Thus, it is overly simplistic to suggest that one of skill in the art could readily substitute Marsili's formulation for Ryan's to result in an efficacious vaccine. There is simply no motivation to modify the references as suggested by the Examiner and there is no reasonable expectation of success.

Thus, the combination cited by the Office does not provide evidence that the claimed invention is a "predictable use of prior art elements according to their established functions." KSR, page 13. Rather, as explained above, the evidence is to the contrary. Those skilled in the art of vaccine formulation are well aware that the efficacy of a vaccine is highly dependent on the particular components, adjuvants and delivery methods used.

Based on the foregoing, applicants submit that the claims are indeed patentable over the cited combination. Accordingly, withdrawal of this basis for rejection is respectfully requested.

Claim 7 was rejected under 35 U.S.C. §103(a) as unpatentable over Ryan in view of Marsili and further in view of U.S. Patent No. 5,614,382 to Metcalf ("Metcalf") and Podda et al.,

*Ann. Ig.* (1991) 3:79-84 ("Podda"). Ryan and Marsili are applied as above. Metcalf allegedly teaches "CRM197 is a non-toxic form of diphtheria toxin which is immunologically indistinguishable from the diphtheria toxin." Podda is said to teach "CRM197 to be an ideal candidate to substitute diphtheria toxoid in a vaccine." Office Action, page 5. However, applicants respectfully submit claim 7 is patentable over the cited art and traverse the rejection and the supporting remarks.

As explained above, the combination of Ryan and Marsili is not believed to render the claims obvious as Ryan does not describe the production of a trivalent vaccine and Marsili's vaccine is formulated for injection as opposed to intranasal delivery and uses a different adjuvant. Metcalf and Podda do not cure the defects of Ryan and Marsili. In particular, Metcalf merely describes the production of CRM197. There is no discussion regarding vaccine formulations where CRM197 acts as an antigen and no description of adjuvants. In fact, the passage of Metcalf referred to in the Office Action explains that CRM197 is used as a carrier for saccharides and is "currently being used in the *Haemophilus influenzae* type b oligosaccharide CRM197 conjugate vaccine." Thus, CRM197 is used for a completely different purpose than in the present vaccine. There is no suggestion to use CRM197 in a vaccine formulation as claimed in the present application.

Podda does not fill the missing gaps. Podda, does not relate to a trivalent vaccine. Rather, Podda's vaccine includes a tetanus toxoid and CRM197. Podda's vaccine, as with Marsili's is formulated for injection and uses Alum as an adjuvant. See, page 80, column 2, second full paragraph of Podda. As explained above, immunological adjuvants have differing mechanisms of action and immune responses to particular antigens are highly dependent on the type of adjuvant selected. Thus, no analogy can be made between Podda's CRM197-containing vaccine and applicants' trivalent vaccine formulated for intranasal delivery with LT-K63 or LT-R72.

Applicants submit the Examiner has chosen bits and pieces of the cited references to arrive at the allegation that this combination of references suggests the claimed invention. This is improper. As stated in *KSR*, "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art."

*KSR*, page 14. The Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. See, e.g., *In re Kotzab*, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000). Thus, a rejection cannot be predicated on the mere identification of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner.

For at least the above reasons, withdrawal of the rejection of claim 7 under 35 U.S.C. §103(a) is respectfully requested.

#### **CONCLUSION**


Applicants submit the claims define a patentable invention and that a Notice of Allowance is therefore in order. If the Examiner notes any further matters which may be resolved by a telephone interview, the Examiner is encouraged to contact Helen Lee by telephone at 510-923-2192.

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## Improving Vaccine Performance with Adjuvants

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New vaccines are presently under development and in testing for the control of infectious diseases, including human immunodeficiency virus (HIV) and tuberculosis. Several of these vaccines are composed of synthetic, recombinant, or highly purified subunit antigens. Subunit vaccines are designed to include only the antigens required for protective immunization and to be safer than whole-inactivated or live-attenuated vaccines. However, the purity of the subunit antigens and the absence of the self-adjuncting immunomodulatory components associated with attenuated or killed vaccines often result in weaker immunogenicity. Immunologic adjuvants are agents that enhance specific immune responses to vaccines. Formulation of vaccines with potent adjuvants is an attractive approach for improving the performance of vaccines composed of subunit antigens. Adjuvants have diverse mechanisms of action and should be selected for use on the basis of the route of administration and the type of immune response (antibody, cell-mediated, or mucosal immunity) that is desired for a particular vaccine.

An immunologic adjuvant may be defined as any substance that, when incorporated into a vaccine formulation, acts generally to accelerate, prolong, or enhance the quality of specific immune responses to vaccine antigens. The word *adjuvant* is derived from the Latin verb *adjuvare*, which means to help or aid. Adjuvant mechanisms of action include the following: (1) increasing the biological or immunologic half-life of vaccine antigens; (2) improving antigen delivery to antigen-presenting cells (APCs), as well as antigen processing and presentation by the APCs; and (3) inducing the production of immunomodulatory cytokines. Through modulation of cytokine responses, adjuvant formulations can be designed that favor the development of T-helper type 1 (Th1) or type 2 (Th2) immune responses to vaccine antigens. Novel adjuvants are presently undergoing preclinical and clinical testing with human candidate vaccines, including experimental subunit vaccines against tuberculosis [1]. Standardized preclinical adjuvant-safety tests to support the clinical evaluation of novel adjuvants are also under development.

Immunologic adjuvants have been under development and in testing for most of this century. In the mid-1920s, Ramon [2, 3] observed that horses that developed abscesses at the site of an injection of diphtheria toxoid produced higher antitoxin titers than animals without abscesses. He later reported that abscesses induced by the injection of foreign substances together with toxoid also augmented antitoxin responses in horses. In 1926, Glenn [4] demonstrated the adjuvant activity

of aluminum compounds with use of an alum-precipitated diphtheria toxoid vaccine.

In the mid-1930s, Freund [5] developed a powerful immunologic adjuvant composed of a water-in-mineral-oil emulsion and containing killed mycobacteria as an additional immunomodulator. This adjuvant is known as Freund's complete adjuvant (FCA), and although it is one of the most effective adjuvants known, it is highly reactogenic and cannot be used in human vaccines. However, Freund's incomplete adjuvant, which does not contain mycobacteria, was employed in an influenza vaccine licensed in the United Kingdom and is used in several HIV vaccines under clinical evaluation.

In 1956 Arthur Johnson discovered the adjuvant activity of endotoxins from gram-negative bacteria [6], and in 1974 Ellouz et al. [7] identified muramyl dipeptide as the smallest adjuvant-active component of the mycobacteria in Freund's complete adjuvant. Presently, aluminum salt-based adjuvants continue to be the only immunologic adjuvants used in United States-licensed vaccines. However, hundreds of natural and synthetic compounds have been identified that have adjuvant activity. A number of these novel adjuvants, which may be used to augment or replace alum in human vaccines, have been under development and in preclinical evaluation for several decades [8]. In animal models, many novel adjuvants have been demonstrated to be more effective than alum in enhancing both antibody and cell-mediated immune responses to vaccine antigens. Extensive preclinical evaluation of novel immunologic adjuvants have been conducted, and clinical trials comparing the activities of various adjuvants have been initiated.

### Advantages of the Use of Adjuvants

Potential advantages of the use of immunologic adjuvants in vaccine formulations include their ability (1) to direct and

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optimize immune responses that are appropriate for the vaccine; (2) to enable mucosal delivery of vaccines; (3) to promote cell-mediated immune responses; (4) to enhance the immunogenicity of weaker immunogens, such as highly purified or recombinant antigens; (5) to reduce the amount of antigen or the frequency of immunization required to provide protective immunity; and (6) to improve the efficacy of vaccines in individuals with reduced or weakened immune responses, such as newborns, the aged, and immunocompromised vaccine recipients.

### Types of Immunologic Adjuvants

Immunologic adjuvants can be classified by their sources, mechanisms of action, and physical or chemical properties. Table 1 lists examples of the types of adjuvants under development and in testing for use with human vaccines.

### Adjuvant Mechanisms of Action

Adjuvants have diverse mechanisms of action and must be chosen for use with a particular vaccine on the basis of the route of administration to be employed and the type of immune responses desired. The first mechanism of adjuvant action identified was the so-called depot effect, in which gel-type adjuvants, such as aluminum hydroxide, or emulsion-based adjuvants, such as Freund's incomplete adjuvant, associate with antigen and facilitate transport of antigen to the draining lymph node, where immune responses are generated. Immunogenicity of small antigens such as synthetic peptides that otherwise would be rapidly cleared from the injection site and from draining lymph nodes can be improved by the use of adjuvants that form particles or otherwise associate with and hold antigen.

Adjuvants can also act through enhancement of antigen presentation. Immunologic adjuvants act directly or indirectly on APCs, such as macrophages and dendritic cells [48, 49]. The emulsion-based adjuvant MF59 has recently been shown to be internalized by dendritic cells [22]. Certain novel adjuvants, such as purified saponins, immunostimulatory complexes, and liposomes, have been shown to greatly improve the induction of major histocompatibility complex (MHC) class I-restricted CD8<sup>+</sup> cytotoxic T lymphocyte (CTL) responses over that induced by the same antigen given alone or in combination with standard alum adjuvants [33, 50–53].

These adjuvants may induce CTL responses by delivering antigen directly to the cytosol for presentation with MHC class I molecules [49]. Cytosolic antigen delivery by membrane-active adjuvants could mimic antigen presentation that occurs during viral infection or immunization with live-attenuated vaccines. Antigen presented to the cytosol could bypass endosomal antigen delivery and subsequent processing with MHC class II molecules, which occurs when antigen is delivered alone or in alum and induces primarily antibody responses [54] via presentation to CD4<sup>+</sup> T helper lymphocytes. Adjuvants may also

**Table 1.** Types of immunologic adjuvants.

Type, adjuvant	Reference
<b>Gel-type</b>	
Aluminum hydroxide or aluminum phosphate	[4, 9]
Calcium phosphate	[9]
<b>Microbial</b>	
DNA CpG motifs	[10]
Monophosphoryl lipid A	[11]
Cholera toxin	[12, 13]
<i>Escherichia coli</i> heat-labile toxin	[14–16]
Pertussis toxin	[17, 18]
Muramyl dipeptide	[7, 19]
<b>Oil-emulsion and emulsifier-based</b>	
Freund's incomplete adjuvant	[20, 21]
MF59	[22–24]
SAF	[25–27]
<b>Particulate</b>	
Immunostimulatory complexes (ISCOMs)	[21, 26, 28]
Liposomes	[29, 30]
Biodegradable microspheres	[31, 32]
Saponins (QS-21)	[33, 34]
<b>Synthetic</b>	
Nonionic block copolymers	[35, 36]
Muramyl peptide analogues	[19, 37, 38]
Polyporphazene	[39, 40]
Synthetic polynucleotides	[41, 42]
<b>Cytokines</b>	
IFN- $\gamma$	[43]
IL-2	[44]
IL-12	[45–47]

promote cytosolic antigen delivery and MHC class I presentation by enabling antigen to cross endosomal membranes into the cytosol after ingestion of antigen-adjuvant complexes by APCs [55].

Antigen can be targeted to macrophages or dendritic cells by particulate adjuvants such as liposomes. APCs can also be stimulated by adjuvants to secrete immunomodulatory cytokines. Various cytokines induced by adjuvants act on lymphocytes to promote predominantly Th1 or Th2 immune responses [54, 56, 57]. Adjuvants that enhance Th1 immune responses through the induction of IFN- $\gamma$  and delayed-type hypersensitivity also elicit the production of IgG subclasses that fix complement and bind with high affinity to Fc- $\gamma$ I receptors (e.g., IgG2a in mice and IgG1 in humans) [25, 58, 59]. These immunoglobulin subclasses are the most active in complement-mediated lysis and in antibody-dependent cell-mediated-cytotoxicity effector mechanisms.

Several cytokines are under evaluation as vaccine adjuvants, including IL-2, IFN- $\gamma$ , granulocyte-macrophage colony stimulating factor, and IL-12 [43–46, 60]. IL-12 is a recently characterized cytokine that may play a pivotal role in the immunomodulatory activities of various immunologic adjuvants [61]. Jankovic et al. [47] showed that the addition of IL-12 to an alum-adsorbed HIV-1 gp120 vaccine elicited Th1 cytokines and IgG2 and IgG3 antibody responses in mice; the same vaccine without IL-12 induced Th2 cytokines and IgG1 antibody responses. Bacterial toxins with adjuvant activity, such as cholera toxin and pertussis toxin, which preferentially drive Th2-like



responses, have been shown to enhance IgA and IgE [12, 57, 62, 63] antibody production. Adjuvants that drive Th2-like immune responses could enhance protection against mucosal virus transmission by augmenting IgA production.

### Adjuvant Safety

The benefits of incorporating adjuvants into vaccine formulations to enhance immunogenicity must be weighed against the risk that these agents will induce adverse reactions. Local adverse reactions include local inflammation at the injection site and, rarely, the induction of granuloma or sterile abscess formation. Systemic reactions to adjuvants observed in laboratory animals include malaise, fever, adjuvant arthritis, and anterior uveitis [64, 65]. Such reactions often are caused by the interaction of the adjuvant and the antigen itself, or may be due to the type of response to a particular antigen the adjuvant produces, or the cytokine profile the adjuvant produces in an antigen. Therefore, even though separate and extensive pre-clinical toxicological and safety studies have been performed on both the adjuvant and the vaccine antigens, a final safety evaluation of the human candidate vaccine formulation proposed for phase I clinical testing should be conducted.

This evaluation should be conducted in a species of small animal in which the antigen has been found to be immunogenic and that can be reproducibly immunized by the same route proposed for the human clinical trials. The dose and frequency of immunization of the vaccine also should meet or exceed those anticipated for use in the clinical trial. Such a test, recently designed by a collaborative effort between the Center for Biological Evaluation and Research/Food and Drug Administration and the National Institute of Allergy and Infectious Diseases, has been used to evaluate several vaccine formulations containing novel adjuvants [66].

### Future Directions

Adjuvant research is a field that is advancing rapidly, which reflects the high rate at which new adjuvants are being discovered and the better understanding of immune mechanisms possible because of advances in immunobiology. In turn, adjuvants should now be applied to the study of many aspects of basic immunology. For example, adjuvants can be used as a tool to study immune mechanisms, such as antigen presentation by dendritic cells and modulation of immune responses by cytokines and their receptors. Adjuvants can also be employed in vaccine design research, which could assist in identifying the requirements of protective immunity, since different adjuvants vary immune responses to the same experimental antigen. The activities of adjuvants in humans as compared with their effect in small animals should be more fully evaluated. Animal models should be developed that can predict as accurately as possible

the effectiveness in humans of a particular adjuvant when formulated with the desired vaccine antigens.

### Summary

Development of safe and effective vaccines composed of subunit antigens will require the ability to selectively drive appropriate protective immune responses to them. The use of immunologic adjuvants to enhance and direct immune responses to subunit vaccines is a critical component of a rational vaccine design. Adjuvants have diverse mechanisms of action and must be selected for use on the basis of the immune responses (e.g., antibody, mucosal, and CTL) that contribute to the induction of protective immunity. Adjuvants can improve the performance of vaccines by targeting antigen to APCs, eliciting cytokines that direct Th1 or Th2 immune responses, promoting cell-mediated immunity (including CTL responses), and reducing the number of immunizations or the amount of antigen required for protective immunization.

The selection of a vaccine adjuvant should be based on analysis of the potential benefit of the adjuvant in enhancing the immunogenicity of a vaccine, weighed against its risk to induce adverse local or systemic reactions. The severity and prevalence of the disease against which the vaccine is designed to afford protection may also be considered in risk-and-benefit determinations for the use of novel adjuvants. Standardized methods to evaluate adjuvant safety should be implemented for human vaccines that are to be formulated with novel adjuvants.

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# GUIDE FOR ADULT IMMUNIZATION

SECOND EDITION

ACP Task Force on Adult Immunization  
and  
Infectious Diseases Society of America

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minutes. In the United States, only health facilities which agree to meet stringent conditions regarding transportation, handling, storage, and administration of the vaccine have been designated Yellow Fever Vaccination Centers. Yellow fever vaccine is highly effective against both the jungle and urban forms of the disease.

Vaccination is recommended for persons traveling or living in areas where yellow fever infection occurs. A valid International Certificate of Vaccination is a requirement for entry into certain countries where yellow fever occurs, particularly if the traveler is arriving from an endemic area. Information regarding infected areas is published annually in *Health Information for International Travelers*. Countries currently reporting yellow fever are noted biweekly in *Summary of Health Information for International Travelers*. Both publications are received by all state and many county and city health departments.

Vaccination is also recommended for laboratory personnel who might be exposed to wild and vaccine strains of yellow fever virus.

#### Administration and Adverse Reactions

A single dose (0.5 mL) of reconstituted yellow fever vaccine given subcutaneously is adequate for primary immunization. Travelers who are vaccinated should also receive a signed and stamped International Certificate of Vaccination. The certificate is valid for 10 years, beginning 10 days after primary immunization and immediately after revaccination.

Reactions to yellow fever vaccine are generally mild. From 2% to 5% of vaccinees develop mild headache, myalgia, low grade fever, and other minor symptoms 5 to 10 days after vaccination. Fewer than 0.2% have to limit their regular activities. Immediate hypersensitivity reactions (for example, rash, urticaria, and asthma) are extremely rare, and occur principally in persons with a history of egg allergy. Although more than 34 million doses of yellow fever vaccine have been distributed, only 2 cases of encephalitis temporally associated with vaccination have been reported in the United States.

#### Precautions and Contraindications

Yellow fever vaccine should not be given to persons who are immunocompromised as a result of immunodeficiency diseases (including HIV infection), leukemia, lymphoma, or generalized malignancy or who are immunosuppressed as a result of therapy with corticosteroids, alkylating drugs, antineoplastic, or radiation.

Although specific information is not available regarding adverse effects of yellow fever vaccine on the developing fetus, it is prudent to avoid vaccinating pregnant women and to advise postponing travel to

areas where yellow fever occurs until after delivery. However, for pregnant women who must travel to areas where the risk for yellow fever is high, immunization is recommended in the belief that the risk of infection outweighs the small theoretical risk from vaccination.

Because yellow fever vaccine is produced in chick embryos, persons with a history of anaphylactic hypersensitivity to eggs should not be vaccinated. Infants under 4 months of age are more susceptible to serious adverse reactions (encephalitis) than older children and should not be immunized. The risk of serious complications in infants appears to be age-related. Whenever possible, vaccination should be delayed until at least 9 months of age.

Recent studies indicate that persons given yellow fever and cholera vaccines simultaneously or 1 to 3 weeks apart develop lower than normal antibody responses to both vaccines. Unless there are time constraints, the two vaccines should be administered separately at a minimal interval of 3 weeks. If the vaccines cannot be administered at least 3 weeks apart, they should be given simultaneously. Yellow fever vaccine can be given simultaneously with up to 5 mL of immune globulin without losing its effectiveness. Chloroquine inhibits the replication of yellow fever virus *in vitro*, but does not adversely affect the antibody response to the vaccine in persons who are taking chloroquine as antimalarial prophylaxis.

#### Revaccination

In persons with continued exposure to yellow fever, a booster dose (0.5 mL, subcutaneously) is indicated at 10-year intervals.